DOI: 10.1002/chem.200902790

Asymmetric Hydrogenation with Water/Silane as the Hydrogen Source

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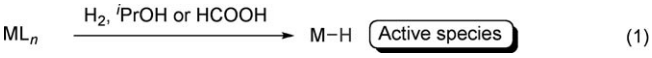
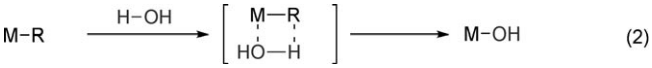
Catalytic asymmetric hydrogenation of prochiral compounds is one of most efficient methods to produce enantiopure compounds.[1] In recent decades, great success has been achieved in the asymmetric hydrogenation of ketones, imines, alkenes, and aromatic compounds[2] with excellent enantioselectivity by using hydrogen gas,[3] *i*PrOH,[4] HCOOH,[5] and Hantzsch esters[6] as the hydrogen source [see Eq. (1)]. For asymmetric hydrogenation, the formation



(1)

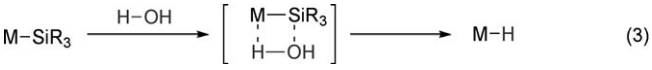
and reactivity of metal–hydride bonds (M–H) are the core topic. In general, active metal–hydride bonds can be formed by the reaction of transition-metal catalysts and the above-mentioned hydrogen sources through homolytic or heterolytic processes. However, reactivities and enantioselectivities are generally substrate dependent. Because there is no omnipotent catalyst for every substrate, new strategies for the formation of active metal–hydride bonds under mild conditions, especially under autoclave-free conditions, are highly desirable.

Water, the most abundant environmentally benign source in nature, has been used in organic synthesis as a reaction reagent and a reaction medium.[7] Despite advances in these areas, water is far less explored as a reaction substrate in asymmetric catalysis. To the best of our knowledge, there are no reports of asymmetric hydrogenation occurring with water as the hydrogen source. In general, it is very difficult for water to donate hydride owing to the oxyphilicity of the central metal as shown in [Eq. (2)], and as a result, usually



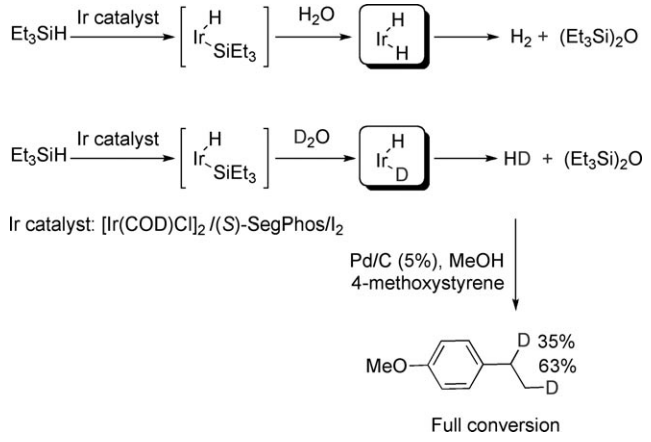
(2)

only metal hydroxides are formed. It is relatively easy to form metal–silyl bonds by the reaction of transition-metal and commercially available silane compounds. Owing to the high oxyphilicity of organic silicon compounds (silica gel is easy to form and widely exists in nature), we envisioned that metal–hydride bonds can be conveniently formed through the reaction of readily available metal–silyl compounds with water as shown in [Eq. (3)], and this method can be applied to asymmetric hydrogenation under mild autoclave-free conditions.



(3)

With this design in hand, triethylsilane and water were selected as model substrates with iridium/bisphosphine as the catalytic system (Scheme 1). No reaction occurred when only triethylsilane was used in the presence of the iridium



Scheme 1. Initial experiments with water as the hydrogen source.

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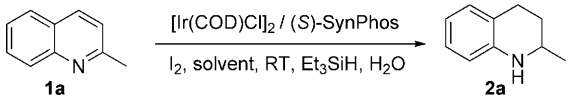
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902790.

catalyst. Hydrogen gas was detected when triethylsilane and water were used. To demonstrate the existence of hydrogen gas, the gas generated from silane and water was transferred to another reactor containing 4-methoxystyrene and Pd/C in methanol; the result showed that full conversion was observed. When D_2O was used instead of water, analysis by NMR spectroscopy showed that 35% of deuterium had been incorporated at the α position and 63% at the β position. A total of 98% (35+63%) deuterium incorporation implied that one hydride was from silane and the other was from water. The other product, $(Et_3Si)_2O$, was confirmed by GC–MS and ^1H NMR spectroscopy. The above experiments demonstrated that hydrogenation with water as the hydrogen source is feasible.

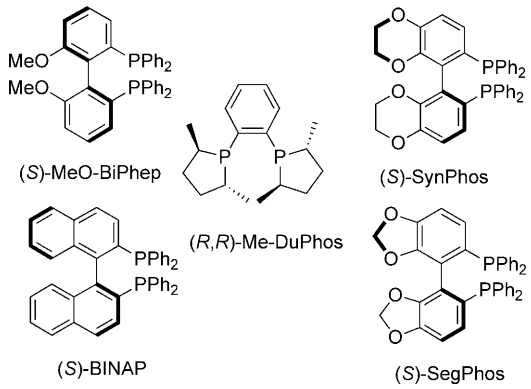
Encouraged by these results, we extended this strategy to the asymmetric hydrogenation of heteroaromatic compounds.[2,8,9] Thus, 2-methylquinoline was selected as a model substrate for condition optimization. First, the reaction was run by using the $[Ir(COD)Cl]_2$/(*S*)-SynPhos/I_2 system as the catalyst in toluene at room temperature (Table 1, entry 1 and Scheme 2) from which **2a** was obtained in 24% yield and 70% *ee* in the presence of 2.0 equivalents of water. The experiment showed that asymmetric hydrogenation could occur with water as the hydrogen source.

Table 1. Ir-catalyzed asymmetric hydrogenation of **1a**.[a]



Entry	Solvent	Ligand	Yield [%][b]	*ee* [%][c]
1	toluene	(*S*)-SynPhos	24	70
2	CH_2Cl_2	(*S*)-SynPhos	11	84
3	EtOAc	(*S*)-SynPhos	46	86
4	acetone	(*S*)-SynPhos	62	73
5	THF	(*S*)-SynPhos	89	87
6	THF	(*S*)-MeO-BiPhep	89	83
7	THF	(*R*,*R*)-Me-DuPhos	41	2
8	THF	(*S*)-BINAP	86	71
9	THF	(*S*)-SegPhos	92	91

[a] Conditions: **1a** (0.25 mmol), $[Ir(COD)Cl]_2$ (1 mol%), ligand (2.2 mol%), I_2 (10 mol%), Et_3SiH (6.0 equiv), H_2O (2.0 equiv), solvent (3 mL), 24 h, RT. [b] Based on **1a**. [c] Determined by chiral HPLC analysis.

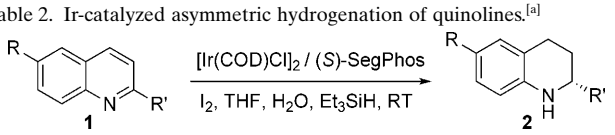


Scheme 2. The various chiral bisphosphine ligands used.

Next, the effect of solvent on reactivity and enantioselectivity was examined. The results showed that the reaction was highly solvent dependent (Table 1, entries 1–5). The highest enantioselectivity (87% *ee*) with good reactivity was obtained in THF. Subsequently, a series of commercially available chiral bisphosphine ligands were screened for the asymmetric hydrogenation reaction (Table 1, entries 5–9 and Scheme 2), and it was found that (*S*)-SegPhos gave the best result.

Having established the optimal conditions, the scope of the Ir-catalyzed asymmetric hydrogenation of quinolines was explored (Table 2). A series of 2-substituted quinolines

Table 2. Ir-catalyzed asymmetric hydrogenation of quinolines.[a]



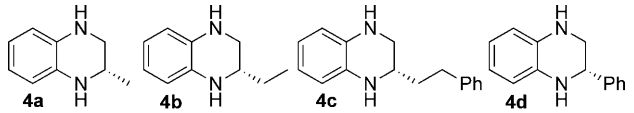
Entry	R/R′	Time [h]	Yield [%][b]	*ee* [%][c]
1	H/Me	24	92 (**2a**)	91 (*S*)
2	H/Et	24	95 (**2b**)	92 (*S*)
3	H/*n*Pr	24	93 (**2c**)	90 (*S*)
4	H/*n*Bu	24	94 (**2d**)	93 (*S*)
5	H/*n*pentyl	24	96 (**2e**)	88 (*S*)
6	H/phenethyl	24	98 (**2f**)	85 (*S*)
7	F/Me	24	97 (**2g**)	87 (*S*)
8	Me/Me	48	90 (**2h**)	93 (*S*)
9	MeO/Me	72	73 (**2i**)	88 (*S*)
10	H/Ph	72	83 (**2j**)	57 (*R*)
11	H/Bn	48	89 (**2k**)	90 (*R*)
12	H/$Me_2C(OH)CH_2$–	24	84 (**2l**)	87 (*R*)
13	H/3,4-$(OCH_2O)C_6H_3(CH_2)_2$–	48	94 (**2m**)	86 (*S*)
14	H/3,4-$(MeO)_2C_6H_3(CH_2)_2$–	48	84 (**2n**)	83 (*S*)

[a] Conditions: **1** (0.25 mmol), $[Ir(COD)Cl]_2$ (1 mol%), ligand (2.2 mol%), I_2 (10 mol%), Et_3SiH (6.0 equiv), H_2O (2.0 equiv), THF (3 mL), RT. [b] Based on **1**. [c] Determined by HPLC.

were smoothly hydrogenated to give the desired products in excellent yields with 88–93% *ee* (Table 2, entries 1–5). 2-Arenethyl-substituted quinolines were also hydrogenated with good asymmetric induction (Table 2, entries 6, 13, and 14). For the substrate with an electron-donating group, only moderate reactivity was obtained (Table 2, entry 9). Good stereocontrol (87% *ee*) was achieved for the substrate that had a free hydroxyl (Table 2, entry 12). For 2-benzylquinoline, the reaction proceeded well to afford the desired product with 90% *ee*. However, 2-phenylquinoline was hydrogenated with only moderate yield and enantioselectivity (57% *ee*, Table 2, entry 10).

Gratifyingly, the above asymmetric hydrogenation strategy can also be extended to asymmetric hydrogenation of the assorted quinoxaline derivatives. Alkyl- or aryl-substituted quinoxalines can be reduced smoothly with 58–78% *ee* and full conversion under the above optimal conditions (see products **4a**–**d** in Scheme 3).

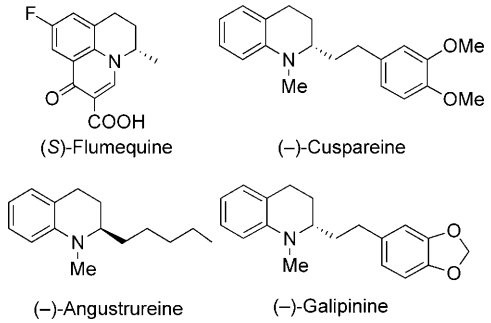
This methodology of Ir-catalyzed asymmetric hydrogenation of quinolines with water/silane provides a convenient route to synthesize optically active tetrahydroquinoline derivatives from very cheap starting materials, quinolines. For



ee: 76%, 92% *ee*: 78%, 97% *ee*: 76%, 95% *ee*: 58%, 91%

Scheme 3. Ir-catalyzed hydrogenation of quinoxalines illustrating the *ee* values and the yields of **4a–d**.

example, the hydrogenation product of 6-fluoro-2-methylquinoline (**2g**) is the key intermediate of the antibacterial agent Flumequine.[10] Importantly, some naturally occurring tetrahydroquinoline alkaloids such as angustrureine, galipinine, and cuspareine were easily synthesized by N-methylation of hydrogenated products (**2e**, **2m**, and **2n**) with the above-mentioned step (Scheme 4).[11,8e–f]



Scheme 4. Some alkaloids and chiral drugs.

In summary, we have developed the first asymmetric hydrogenation with water/silane as the hydrogen source under mild autoclave-free reaction conditions with up to 93% *ee*. For this hydrogenation reaction two hydrides are from silanes and the other two are from water. This methodolgy has been successfully applied to the asymmetric synthesis of some alkaloids and chiral drugs. Further studies on using water as the sole hydride source are in progress.

Experimental Section

Typical procedure for asymmetric hydrosilylation of quinolines: A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*)-SegPhos (3.4 mg, 0.0055 mmol) in THF (1 mL) was stirred at room temperature for 10 min in a Schlenk tube, then I_2 (6.4 mg, 0.025 mmol) was added and stirred for another 10 min. The substrate (0.25 mmol) and Et_3SiH (174 mg, 1.50 mmol) were added, followed by THF (2 mL) with H_2O (9 mg, 0.50 mmol). The resulting mixture was allowed to stir at RT for 24–72 h and monitored by TLC analysis. The reaction mixture was purified by using a silica-gel column and was eluted with ethyl acetate/petroleum ether to give the pure product. The enantiomeric excesses were determined by chiral HPLC analysis.

Acknowledgements

We are grateful for financial support from National Natural Science Foundation of China (20621063), National Basic Research Program of China (2010CB833304) and Dalian Institute of Chemical Physics (K2007F1).

Keywords: asymmetric catalysis · hydrogenation · iridium · quinolines · quinoxalines

[1] a) H.-U. Blaser, B. Pugin, F. Spindler, *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed. (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2000**; Chapter 3.3.1; b) P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**, p. 175; c) *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weiheim, **2007**.

[2] For some reviews on hydrogenation of aromatic compounds, see: a) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Chin. J. Org. Chem.* **2005**, *25*, 634; b) F. Glorius, *Org. Biomol. Chem.* **2005**, *3*, 4171; c) P. J. Dyson, *Dalton Trans.* **2003**, 2964; d) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; e) R. Kuwano, *Heterocycles* **2008**, *76*, 909.

[3] For selected reviews, see: a) R. Noyori, *Angew. Chem.* **2002**, *114*, 2108; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; c) J. M. Brunel, *Recent Res. Dev. Org. Chem.* **2003**, *7*, 155; d) P. Liu, H.-F. Jiang, *Chin. J. Org. Chem.* **2004**, *24*, 1317; e) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; f) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40; *Angew. Chem. Int. Ed.* **2001**, *40*, 40; g) W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998; h) K. Rossen, *Angew. Chem.* **2001**, *113*, 4747; *Angew. Chem. Int. Ed.* **2001**, *40*, 4611; i) C. Jäkel, R. Paciello, *Chem. Rev.* **2006**, *106*, 2912.

[4] For selected reviews, see: a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97; b) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry* **1999**, *10*, 2045; c) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051.

[5] For selected reviews, see: a) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226; b) T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393; c) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237.

[6] For selected reviews, see: a) S.-L. You, *Chem. Asian J.* **2007**, *2*, 820; b) C. Wang, X. Wu, J. Xiao, *Chem. Asian J.* **2008**, *3*, 1750; c) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407.

[7] For recent examples, see: a) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936; b) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687; c) G. J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Science* **2000**, *287*, 1636; d) S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275; e) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972; *Angew. Chem. Int. Ed.* **2006**, *45*, 958.

[8] For recent examples of the asymmetric hydrogenation of quinolines, see: a) M. Rueping, T. Theissmann, S. Raja, J. W. P. Bats, *Adv. Synth. Catal.* **2008**, *350*, 1001; b) H.-F. Zhou, Z.-W. Li, Z.-J. Wang, T.-L. Wang, L.-J. Xu, Y.-M. He, Q.-H. Fan, J. Pan, L.-Q. Gu, A. S. C. Chan, *Angew. Chem.* **2008**, *120*, 8592; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464; c) D.-W. Wang, X.-B. Wang, D.-S. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2009**, *74*, 2780; d) Q.-S. Guo, D.-M. Du, J. Xu, *Angew. Chem.* **2008**, *120*, 771; *Angew. Chem. Int. Ed.* **2008**, *47*, 759; e) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683; f) S.-M. Lu, Y.-Q. Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem.* **2006**, *118*, 2318; *Angew. Chem. Int. Ed.* **2006**, *45*, 2260; g) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536; h) X.-B. Wang, Y.-G. Zhou, *J. Org. Chem.* **2008**, *73*, 5640;

i) Z.-W. Li, T.-L. Wang, Y.-M. He, Z.-J. Wang, Q.-H. Fan, J. Pan, L.-J. Xu, *Org. Lett.* **2008**, *10*, 5265; j) S.-M. Lu, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 1101; k) M. T. Reetz, X.-G. Li, *Chem. Commun.* **2006**, 2159; l) Z.-J. Wang, G.-J. Deng, Y. Li, Y.-M. He, W.-J. Tang, Q.-H. Fan, *Org. Lett.* **2007**, *9*, 1243; m) W.-J. Tang, S.-F. Zhu, L.-J. Xu, Q.-L. Zhou, Q.-H. Fan, H.-F. Zhou, K. Lam, A. S. C. Chan, *Chem. Commun.* **2007**, 613; n) L. J. Xu, K. H. Lam, J. X. Ji, Q.-H. Fan, W.-H. Lo, A. S. C. Chan, *Chem. Commun.* **2005**, 1390; o) C. Wang, C. Q. Li, X. F. Wu, A. Pettman, J. L. Xiao, *Angew. Chem.* **2009**, *121*, 6646; *Angew. Chem. Int. Ed.* **2009**, *48*, 6524; p) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genet, T. Ohshima, V. Ratovelomanana-Vidal, K. Mashima, *Chem. Eur. J.* **2009**, *15*, 9990; q) Z.-J. Wang, H.-F. Zhou, T.-L. Wang, Y.-M. He, Q.-H. Fan, *Green Chem.* **2009**, *11*, 767.

[9] For selected examples of asymmetric hydrogenation of other aromatic compounds, see: a) R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2007**, *129*, 808; b) C. Y. Legault, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 8966; c) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614; d) P. Feiertag, M. Albert, U. Nettekoven, F. Spindler, *Org. Lett.* **2006**, *8*, 4133; e) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653; f) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213; g) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562.

[10] J. Bálint, G. Egri, E. Fogassy, Z. Böcskei, K. Simon, A. Gajáry, A. Friesz, *Tetrahedron: Asymmetry* **1999**, *10*, 1079.

[11] a) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté, C. Moulis, *Phytochemistry* **1999**, *51*, 1167; b) J. H. Rakotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fourasté, C. Moulis, *Planta Med.* **1998**, *64*, 762; c) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250.

Received: October 29, 2009
Published online: December 9, 2009

